Complications of diabetes: renal disease and promotion of self-management

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Renal complications of type 2 diabetes

Raised blood glucose levels and related microvascular disease are associated with progressive damage to the kidneys. This damage becomes detectable when protein (primarily albumin) is excreted in the urine in higher concentrations than normal. As the severity of the damage increases, the quantity of protein in the urine also increases. When the level of albumin in the urine is fairly low, the condition is known as microalbuminuria or incipient nephropathy; higher albumin excretion is described as proteinuria. Eventually the condition can lead to renal failure.[2]

Epidemiological studies report prevalence rates of microalbuminuria in patients with type 2 diabetes ranging from 8% to 32% with most estimates being around 25%.[4–15] Prevalence estimates for proteinuria range from 5% to 19% with most studies giving rates of around 15%.[5] [6] [9–11] [15] [16] This variation may be a product of the criteria used to define the condition, the stage of the disease, and the methods used to assess it. Figures from the UK Prospective Diabetes Study (UKPDS), based on 3867 patients, suggest that about 12% have microalbuminuria (although using a high threshold) and 1.9% have proteinuria at the time of diagnosis of diabetes.[17] A US study which followed 794 patients with type 2 diabetes who were initially free from proteinuria (defined as ≥30 µg protein/l urine) found that 1.3% developed renal failure within 10 years.[18]

A substantial proportion of patients treated in renal units in the UK have diabetes. Diabetic nephropathy is the most common single cause of renal failure among adult patients starting renal replacement therapy (16% of the total).[19]

RISK FACTORS

The main risk factors are hereditary susceptibility (including ethnic origin), raised blood glucose, and blood pressure. There may be links between diabetic renal disease and smoking, blood lipids, obesity, age, sex, and duration of diabetes.[18] [20–30]

People of Asian or African ethnic origin are particularly susceptible both to type 2 diabetes and to diabetic renal disease. A study of people of Asian (Indian) descent found that they were 13.6 times more likely to require replacement therapy for diabetic renal disease than white Caucasians.[31] Another survey, which included all 5901 patients accepted for renal replacement therapy by renal units in England, found that people of Asian or Afro-Caribbean origin were almost six times as likely as white Caucasians to receive treatment for diabetic renal failure.[32] Close relatives of patients with diabetic renal disease are much more likely than others to develop the condition; odds ratios of 3.8 (95% CI 1.4 to 10.4)[33] and 8.1 (95% CI 2.2 to 29.6)[34] have been reported.

The majority of studies of blood glucose found associations between higher glycaemia and risk of renal disease.[17] [18] [20] [21] [23] [35]

Studies involving >4000 participants in total have reported links between raised blood pressure (systolic, diastolic or both) and diabetic renal disease.[18] [21] [26–28] [35] Advancing renal disease can lead to increased blood pressure, while increased blood pressure accelerates the course of diabetic renal disease.

Patients with diabetic retinopathy are also more likely to develop renal disease.[23] [25]

DISEASE PROGRESSION AND MORTALITY

Longitudinal studies suggest that, while protein excretion tends to increase over time, the rate and direction of change varies between individuals.[22] [36] Fewer than 5% of deaths in patients with type 2 diabetes are directly attributed to renal disease[37] [38]; most result from myocardial infarction, heart failure, or stroke. However, a meta-analysis of eight studies found that the death rate in patients with microalbuminuria was over twice the rate in those with normal urinary albumin (risk ratios 2.4 (95% CI 1.8 to 3.1) and 2.0 (95% CI 1.4 to 2.7) for overall and cardiovascular mortality, respectively).[39] A 12 year study of 4714 patients with diabetes (both types) reported that proteinuria was associated with an eightfold increase in deaths in women and a fivefold increase in men.[40]

IDENTIFYING PATIENTS WITH RENAL DISEASE

Urine tests are used to detect and monitor diabetic renal disease. They may measure albumin alone or allow an albumin:creatinine ratio to be calculated. Some are suitable for near patient testing (side room tests) while others require sophisticated laboratory equipment. The former are less accurate but are quicker and easier to use; seven of these are available in the UK.

Evidence was found on the accuracy of the Micral-Test II, Albustix, and Microbumintest. No direct comparisons were identified and there is no evidence that any product is more accurate than others. Sensitivity figures ranged

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from 51%[41] to 100%[42–44] and specificity from 27%[45 46] to 97%,[47 48] but different methods, reference standards, ranges, and thresholds were used for these assessments. Any attempt to determine the most effective test is hampered by the heterogeneity of the evidence.

Laboratory tests include radioimmunoassay, immunoturbidimetry, immunonephelometry, enzyme linked immunosorbent assay (ELISA), and the DCA 2000 microalbumin/creatinine assay system. Studies assessing the albumin concentration in urine produced sensitivity and specificity levels above 90% in only two out of 11 studies,[2 7 49–54] one using radioimmunoassay in an early morning sample[55] and the other using immunonephelometry in a random sample.[53] Two studies of ELISA in early morning samples[7 49] and one using immunoturbidimetry in overnight samples[50] reported sensitivity of over 80% and specificity of over 90%. In three studies[7 51 52] the sensitivity or specificity levels fell below 80%.

All studies of tests measuring albumin:creatinine ratios reported sensitivity and specificity levels above 90%.[7 49 50 52 55–59] Accurate measurements were demonstrated with early morning, overnight, and 24 hour samples but the ELISA test on random urine samples achieved only 80% sensitivity and 81% specificity.[7]

These tests differ in their nature and have been assessed by methods which may not be directly comparable, so it is not clear which is the most effective or useful. Furthermore, there is very marked day to day variation in urinary albumin excretion and other illness can increase albumin excretion, so a single test on a single day is not reliable. Considered as a whole, the evidence suggests that health professionals should use urine tests on several occasions each year. They should not rely on a single near-patient test to assess diabetic renal disease.

An unpublished British Diabetic Association audit of 47 districts found that 64% (range 20–96) of patients known to have type 2 diabetes had a renal function test in 1998.

INTERVENTIONS TO REDUCE RENAL COMPLICATIONS OF DIABETES

The evidence discussed in this section comes from randomised controlled trials which focus on antihypertensive drugs, blood glucose control, reducing dietary protein, and lipid reducing drugs.

Antihypertensive treatment

Renal disease was among the outcomes assessed in the UKPDS 38 trial of blood pressure control in patients with type 2 diabetes.[60] This trial randomised 1148 people to tight or less tight blood pressure control and followed them for a median period of 8.4 years. The mean blood pressure in the two groups was 144/82 and 154/87, respectively. The tight control group had less microvascular disease with a relative risk (RR) for the aggregate end point (which included retinopathy, vitreous haemorrhage, and renal failure) of 0.63 (95% CI 0.44 to 0.89). A trend for reduced renal disease

was not statistically significant (RR 0.35, 99% CI 0.03 to 3.66 and 0.58, 99% CI 0.15 to 2.21 for fatal and non-fatal renal disease, respectively). Five of six surrogate outcomes favoured tight control but only the proportion with microalbuminuria at six years achieved statistical significance (20.3% with tight control versus 28.5% with less tight control; RR = 0.71, 99% CI 0.51 to 0.99).

ACE inhibitors

Particular attention has focused on angiotensin converting enzyme (ACE) inhibitors which reduce constriction of blood vessels, including those in the kidneys. A large international study (n=3577) comparing an ACE inhibitor (ramipril) with placebo in patients with diabetes (98% type 2, mean duration 11 years) reported that ramipril reduced both nephropathy and total mortality by 24% after 4.5 years.[61] All patients had at least one additional cardiovascular risk factor—hypertension, high cholesterol, microalbuminuria, or smoking.

Many smaller studies have been pooled in a series of meta-analyses. Most of these compare different antihypertensive drugs. A meta-analysis which pooled trials lasting more than a week revealed that ACE inhibitors reduce urinary protein levels significantly more than other antihypertensive drugs in both diabetic and non-diabetic patients.[62] The mean change in urinary protein with ACE inhibition was –40% (95% CI –43 to –37) compared with –17% (95% CI –19 to 15) for other drugs. Nifedipine (a dihydropyridine calcium channel blocker) had the smallest effect (–8% (95% CI –13 to –2)).

Another review pooled trials with follow up times over six months.[63] The results again showed that ACE inhibitors reduced urinary protein more than other antihypertensive agents. Analysis of data from 84 trials of mixed designs suggested that the anti-proteinuric effect of ACE inhibitors and non-dihydropyridine calcium channel blockers (verapamil, diltiazem) was greater than could be explained by changes in blood pressure. However, this enhanced benefit was not apparent from the meta-analysis of 14 randomised controlled trials only which found that the effects on urinary protein were proportional to changes in blood pressure.

Two other meta-analyses with different inclusion criteria reinforce these results.[64 65] One reported that ACE inhibitors reduced protein excretion by 25% even when blood pressure remained constant, and that kidney function deteriorated significantly faster in patients with diabetic renal disease treated with nifedipine.[65]

Trials published since these meta-analyses suggest that differences between drugs in their effects on renal function may only be significant in patients who have renal disease. Those with more than 100 patients are discussed below.

The UKPDS 39 study reported no differences between atenolol (a β blocker) and captopril (an ACE inhibitor) in 758 patients.[66] Few of the patients had renal disease and for

two thirds of the study period 60% were taking other antihypertensives as well as (or instead of) the drug to which they had been randomised; 35% of patients on atenolol discontinued treatment because of adverse effects compared with 22% on captopril (p<0.001).

A trial in 314 patients with type 2 diabetes, hypertension, and microalbuminuria found that lisinopril (an ACE inhibitor) reduced albumin excretion significantly more than nifedipine.[67] Similar results were found in a study by De Cesaris *et al*[68] comparing benazapril with nicardipine in 103 patients. Crepaldi *et al*[69] found little difference between lisinopril and nifedipine in 162 patients; although lisinopril seemed to produce greater reduction in albumin excretion in patients with microalbuminuria at baseline (30%), this was not statistically significant.

A meta-analysis of randomised controlled trials by Lovell[70] found that ACE inhibitors reduced albumin excretion in patients with diabetes and microalbuminuria, even when their blood pressure was normal. Other randomised controlled trials which were not included in this meta-analysis but which also compared ACE inhibitors (enalapril, ramipril or perindopril) with placebo in patients with mild hypertension or normal blood pressure, diabetes, and microalbuminuria also found that ACE inhibitors reduced albumin excretion.[71–73] Not only was renal function preserved, but the beneficial effects increased over five years.[72 73]

The evidence therefore demonstrates that ACE inhibitors offer particular benefits for patients with diabetes and renal disease or microalbuminuria, even when normotensive. Dihydropyridine calcium channel blockers such as nifedipine have a less favourable pattern of effects in people with diabetes and renal disease.

Of these trials, only those carried out by the UKPDS assessed renal failure or death rates and none measured quality of life. There seems to be a general and unquestioned assumption that reduction of urinary albumin would inevitably be associated with improvements in such end points. Improvements in surrogate outcome measures such as blood pressure can be associated with deterioration in crucial end points such as life expectancy.[74] Studies of antihypertensive drug treatment in diabetic renal disease should be designed to detect effects on long term morbidity and mortality.

Improved blood glucose control
More intensive control of blood glucose may delay the development of renal disease. The UKPDS 33 study (n=3867) reported that the relative risk of microalbuminuria at nine years was 0.76 (99% CI 0.6 to 0.9) with tight control (mean glycosylated haemoglobin (HbA_{1c}) 7.0%) compared with less tight control (mean HbA_{1c} 7.9%).[17] At 12 years the relative risk fell to 0.67 (99% CI 0.5 to 0.9). It is too soon to know to what degree this may reduce the risk of renal failure.

A Japanese study reported that a mean HbA_{1c} of 7.1% over a period of six years achieved by relatively frequent use of insulin (multiple injection therapy, MIT) reduced the risk of worsening nephropathy by 70% (95% CI 14 to 89) relative to a mean HbA_{1c} of 9.4% in patients on conventional insulin therapy (CIT).[75] Of patients with normal renal function at baseline, 7.7% developed nephropathy in the MIT group and 28% in the CIT group (p=0.032). Among those with microalbuminuria (defined as urinary albumin excretion 30–300 mg/24 h), nephropathy progressed in 11.5% and 32% of the MIT and CIT groups, respectively (p=0.044).

Reduced dietary protein
A systematic review found that a diet containing 0.3–0.8 g/kg body weight of protein per day may slow progression to renal failure in subjects with type 1 diabetes.[76] No reliable evidence was found relating to type 2 diabetes.

Lipid reduction
No conclusive evidence was found that lipid reduction using statins or gemfibrozil affects renal function.[77–80] However, these drugs may be appropriate for reduction of cardiovascular morbidity and mortality in patients with diabetes.[81]

MULTIFACTORIAL INTERVENTION
Four years of intensive multifactorial treatment of patients with microalbuminuria reduced progression of renal disease and improved a range of other diabetes related end points.[82] The intervention involved tight control of blood pressure, glucose and lipids, ACE inhibitors regardless of blood pressure, advice on diet, vitamin supplements, exercise, and help with smoking cessation. 10% of patients in the intensively treated group developed nephropathy compared with 24% in the group which received standard care from GPs (odds ratio 0.27, 95% CI 0.10 to 0.75). Blindness and autonomic neuropathy also developed significantly less often in the intensively treated group.

COSTS
Tight control of blood pressure is highly cost effective. Analysis of figures derived from the UKPDS 38 study (UKPDS 40), using 1997 values, shows that the incremental cost per life year gained was £720 with costs and effects discounted at 6% per year, or £291 with costs, not effects, discounted.[83] The analysis was based on unit costs for all NHS resources used by all patients over the entire period of the trial. Tight blood pressure control reduced the rate of complications requiring hospitalisation, which offset the cost of antihypertensive drugs so that net costs for the two groups were not significantly different.

A model suggests that treating all middle aged subjects with diabetes with ACE inhibitors is more cost effective than screening and treating for microalbuminuria or proteinuria, with a cost of $7500 for each quality adjusted life year gained.[84]

IMPLICATIONS

- The urine of subjects with type 2 diabetes should be tested regularly (at least annually) for proteinuria and, if this is negative, for microalbuminuria. Two or more measurements should be carried out.
- Evidence for the effectiveness of individual near-patient tests used by the NHS is inconclusive.
- The blood pressure of diabetic patients should be checked at regular intervals and treatment offered if it is found to be consistently higher than 140/90.[85]
- In those with levels of urinary albumin above normal, treatment with ACE inhibitors is appropriate even if blood pressure is normal.
- Blood glucose levels should be kept as low as is consistent with an acceptable quality of life.
- Further research is required to establish how dietary protein affects progression of renal disease in type 2 diabetes.

Promotion of self-management

While medical interventions are important in diabetes, long term outcomes depend on choices that patients make themselves. Interventions to help people with type 2 diabetes to change their behaviour fall into to three broad categories: information and skills programmes, cognitive behavioural interventions, and patient empowerment.

These concentrated on everyday diabetes management. Outcome measures included knowledge, skill in diabetes-specific tasks such as glucose testing, adherence to dietary advice, anxiety levels, and rates of hospital admission.

Of 53 relevant randomised clinical trials identified,[3] seven involved follow up of a year or more and 13 randomised 100 or more participants. Only studies meeting at least one of these criteria were discussed in the bulletin. Reported differences achieved statistical significance at the $p<0.05$ level. Although five meta-analyses were also identified, their quality was judged to be too poor for the conclusions to be reliable.[87–91]

INFORMATION AND SKILLS PROGRAMMES

Participants in the DIABEDS study (n=532) had lower weight (184 lb (83.6 kg) versus 187 lb (85 kg)), blood pressure (diastolic 82 versus 84 mm Hg, systolic 142 versus 146 mm Hg) and HbA_{1c} (–0.43% versus +0.53%) than controls after 11–14 months.[92 93]

In a German study of 1139 patients, intensified health education (individual diet and physical activity advice, physical exercise and anti-smoking groups) had no impact on weight after five years, but participants had lower blood pressure (diastolic 87 versus 92 mm Hg, systolic 143 versus 154 mm Hg) than controls.[94]

A study that compared home teaching with usual care in 471 subjects found that the intervention led to higher scores for knowledge and skill after six months.[95] Culture-specific one-to-one education for 201 British Asians produced greater improvements than usual care in knowledge, self-care, and attitudes after six months.[96] After 27 months of a study of six clinic sessions intended to enhance motivation for self-management in 86 subjects, participants used less oral antidiabetic medication than those in the "usual care" group.[97] Monthly telephone calls from nurses in a one year study in 275 subjects led to lower HbA_{1c} and higher patient satisfaction scores than usual care.[98]

A computer intervention in 105 patients offered personalised dietary information or usual care.[99] The intervention group had higher knowledge scores than controls but there were no differences in weight or HbA_{1c}.

Group interventions

Participants in a small UK study (n=75) received either group education with specialist nurses or usual care.[100] After one year the intervention group had higher knowledge scores and had lost more weight than controls (5.5 kg versus 3 kg) but there were no differences in HbA_{1c} levels.

Another UK study randomised 120 obese participants with limited literacy skills to monthly small group meetings with videos and handouts, similar meetings without videos, or lectures.[101] Although participants in the video group lost more weight at seven months, this was not sustained. There were no differences in HbA_{1c}.

One hundred and seventy hospital inpatients received either a two day "Living with Diabetes" group programme or usual care.[102] At four months the intervention group reported better compliance with self-care advice than controls.

Participants (n=120) in an Italian study received either four group meetings focusing on diabetes awareness, foot care and changing behaviour, or usual care.[103] After a year, there were no differences in knowledge, quality of life, weight, or HbA_{1c}.

Overall, these studies suggest that individual or group educational interventions can produce small improvements in knowledge, weight, and blood pressure but the clinical significance of these changes is uncertain.

COGNITIVE AND BEHAVIOURAL INTERVENTIONS

Cognitive/behavioural interventions are relatively intensive programmes based on the principles of learning theory and/or social cognition models.[86] In the context of type 2 diabetes, these usually target weight loss through diet and/or exercise. Programmes involve goal setting, problem solving, modification of self-perceptions, the use of behavioural contracts, and sometimes physical exercise.

Two studies of individual programmes involved more than 100 participants.[104 105] In one the 155 participants were randomised to receive usual care or one of three behavioural interventions over one year.[105] No differences between the groups were found in HbA_{1c} or weight. In an Australian study the 179 participants received individual information sessions, group sessions, or an individual behavioural intervention over one year.[104] There were no differences in knowledge, satisfaction, HbA_{1c}

levels, or systolic blood pressure but the behavioural intervention group had a slightly greater fall in diastolic blood pressure at 12 months (8 mm Hg versus 5 mm Hg).

A study involving 206 participants compared a brief office based computer intervention with usual care.[106–108] A computer assessment was followed by usual care or another assessment and behavioural strategies. After a year there were no differences in weight or HbA$_{1c}$.

In a group intervention study the 76 participants received cognitive/behavioural interventions (diet plus exercise, diet alone, or exercise alone) or information only.[109] After 18 months there were no differences in weight but the diet plus exercise group had lower HbA$_{1c}$ than controls (7.7% versus 8.6%). In addition, both the combination and diet only groups reported higher quality of life than controls.

In another group study 53 participants were randomised to behaviour modification (16 weekly meetings), nutrition education (16 weekly meetings), or usual care (4 monthly meetings).[110] There were no differences between groups in weight, physiological measures, eating, or exercise behaviour at 16 months.

Participants (n=101) who received either the "Sixty Something" programme or usual care were assessed immediately after the intervention.[111] The intervention led to better self-care behaviour and greater weight loss at the end of the programme (–5.8 lb (2.6 kg) versus +1.4 lb (0.6 kg)) but not at follow up (–1.9 lb (0.9 kg) versus –3.5 lb (1.6 kg)). There were no differences in HbA$_{1c}$ levels or measures of self-efficacy or mood.

A trial in 55 subjects investigated cognitive/behaviour therapy to improve diet and encourage exercise.[112] Participants in the behaviour modification group lost the most weight, but there were no differences in HbA$_{1c}$ levels.

In summary, only one study of a cognitive or behavioural intervention found sustained weight loss,[112] and one reduced HbA$_{1c}$ levels.[109] No evidence was found to suggest that either individual or group methods were superior.

PATIENT EMPOWERMENT

These programmes aim to enhance participation in diabetes management, but no reliable evidence was found to support the techniques assessed.[113] [114]

IMPLICATIONS
- Interventions should take into account such factors as age, educational level, and ethnic origin.
- Further research is necessary to determine whether specific interventions to promote self-management have clinically significant long term effects on HbA$_{1c}$ levels, morbidity, quality of life, and mortality.

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